

# **Carcinosarcoma of Ovary, it's Histopathological, Management and Prognostic Analysis with Review of Literature**

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## **Authors' contributions**

*This work was carried out in collaboration between both authors. Author RN contributed in literature search, manuscript preparation and design. Author TKS contributed in concept, literature research, manuscript preparation, editing and review. Both authors read and approved the final manuscript.*

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**Review Article**

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## **ABSTRACT**

Carcinosarcoma is a mixed malignant biphasic tumour representing a rare entity and comprises of both epithelial and mesenchymal components. Primary ovarian carcinosarcoma is a rare neoplasm with a number of cases reported in the literature in the hundreds. It accounts for less than 1% of all ovarian tumours. These tumours are usually diagnosed at older age and advanced stage. It has aggressive clinical behaviour and survival depends on stage at presentation. Radiological imagings cannot differentiate carcinosarcomas from other ovarian cancers. Diagnosis is based upon histological findings. Cytoreductive debulking surgery is a crucial part in the treatment of carcinosarcoma of ovary. The role of adjuvant chemotherapy regimen is still controversial. Combination chemotherapy with taxane and platinum based regimen or ifosfamide and platinum based regimen are considered as adjuvant treatment. Despite aggressive treatment modalities such as surgery and chemotherapy, the outcome is poor. Response to therapy and overall survival for

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carcinosarcoma are poor in comparison to that of epithelial ovarian malignancies. Due to rarity of the disease, such poor prognosis needs collaboration of studies with molecular analysis to obtain new therapeutic guidelines to improve survival of the patients.

**Keywords:** Carcinosarcoma; chemotherapy; cytoreductive surgery; heterologous elements; prognosis; ovary.

## 1. INTRODUCTION

Ovarian cancer is the second most common gynaecologic cancer and is one of the most lethal female malignancies [1]. Sarcomas are rare malignancies of ovary. Carcinosarcoma, leiomyosarcoma, rhabdomyosarcoma, fibromyosarcomas and angiomyosarcomas are the possible different types of sarcomas in ovary [2]. Carcinosarcoma is the most frequent subgroup among these. Ovarian carcinosarcoma is a rare subtype of ovarian cancer with an aggressive behaviour and poor prognosis. Survival of ovarian carcinosarcoma in both early and late stage is inferior to serous ovarian carcinomas [3]. In female genital tract it is commonly seen in uterus but ovarian location is a rare entity. Peritoneal, fallopian tubes, cervical and vaginal carcinosarcomas are rarely seen [4]. Ovarian carcinosarcoma is also known as malignant mixed mullerian tumours (MMMT). The majority occur in postmenopausal women and only 10% of cases occur only in younger women [5]. Obesity, nulliparity, exogenous oestrogen and long term tamoxifen use are the possible risk factors for MMMTs [6]. There are no standard guidelines for the treatment. The data published in the literatures are only retrospective reviews and few institutions are able to do prospective studies. According to some studies, optimal cytoreductive surgery followed by adjuvant chemotherapy may be associated with improved survival [7-10]. The purpose of the review is to compare and give an extensive idea from the published data regarding management and prognosis of the disease.

## 2. INCIDENCE

Ovarian cancer is the fifth leading cause of cancer related death among women and 22,280 cases with 15,500 deaths were reported in 2012 [11]. The majority are epithelial types with serous subtype being the most common. Carcinosarcoma is a rare histological subtype of ovarian malignancy and is diagnosed in 1-4% among all ovarian cancer survivors [12-17]. Carcinosarcoma of the ovary is nearly three times less prevalent than that of uterus [18]. The majority is seen in Caucasian and present at

advanced stages [7]. Fewer than 400 cases have been reported in the literature [15]. Carcinosarcoma predominantly occurs in postmenopausal women with low parity [19] and the mean age of presentation is 65 years [15]. Pelvic irradiation may increase the incidence of MMMT [20].

## 3. HISTOGENESIS

A recent study shows a monoclonal theory of histogenesis in ovarian carcinosarcomas. According to this, metaplastic transformation of the epithelial component causes tumourigenesis resulting in formation of sarcomatous component [21]. But, high rate of recurrence in MMMT of ovary treated with platinum based regimen suggests insufficiency of the theory. Further study on molecular characteristics is necessary to develop knowledge regarding specific targeted therapies to increase survival outcome.

Three theories try to explain the histogenesis of MMMTs [5]:

- Combination theory: It suggests that both cellular lines come from the same stem cell.
- Collision theory: It proposes that two different cellular lines with different mutations generate the tumour.
- Conversion theory: It suggests that a cellular line already carrying the mutation suffers a metaplastic transformation, producing a further cellular clone.

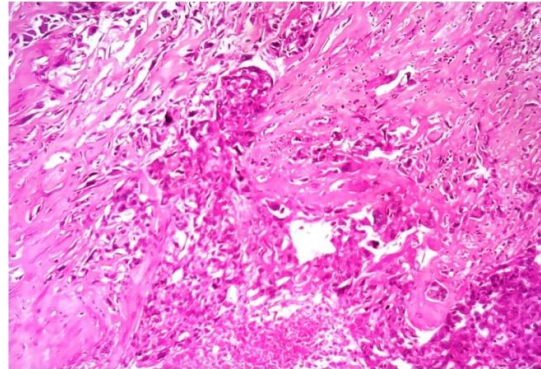
## 4. HISTOPATHOLOGY

On gross examination, carcinosarcomas are composed of soft to firm, gray or tan solid tissues with prominent areas of hemorrhage, necrosis and cystic degeneration [19]. Occasionally, bone or cartilage may be found on palpation. Histopathologically, it is composed of both carcinomatous and mesenchymal components (Fig. 1). Sarcomatous component can be homologous (composed of tissues that normally found in ovary) or heterologous (composed of tissues not normally found in ovary) based on origin of its mesenchymal tissue [22].

Homogenous part may be endometrial stromal sarcoma, fibrosarcoma, and leiomyosarcoma. Heterogeneous part may be chondrosarcoma, rhabdomyosarcoma, and osteosarcoma [23]. Carcinomatous components are usually high grade [19] and can be serous, endometrioid, undifferentiated carcinoma, clear cell carcinoma or squamous cell carcinoma [13,20,24]. Epithelial components mostly present in multiple forms and serous subtypes are more common than endometrioid subtypes with an inferior prognosis [25]. Clear cell and squamous cell subtypes are rarely seen. In the majority of cases epithelial components are responsible for tumour progression and distant metastases [26]. Homologous sarcomatous components do not carry a better prognosis than heterologous sarcomatous components [25,27-29]. Histopathological components in carcinosarcoma of ovary are described in Fig. 2 in schematic form.

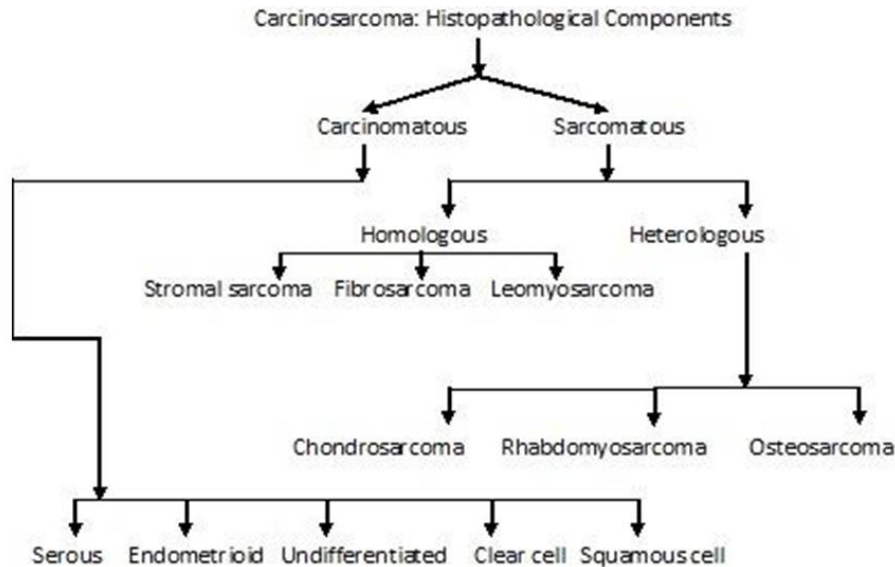
According to Boucher et al. [22] equal representation of the epithelial endometrioid and serous component types in ovarian carcinosarcomas and mesenchymal component is largely heterologous, of chondromatous and rhabdomyoblastic differentiation. According to Kunkel et al. [30] serous carcinomatous components are overwhelming and also a predominance of heterologous chondromatous components is noted. Menon et al. [31] found endometrioid carcinoma and heterologous rhabdomyosarcoma as predominant components. According to Patnayak et al. [32]

serous carcinoma as predominant epithelial component and rhabdomyosarcoma as predominant sarcomatous component are identified. Rama K et al. [6] in a recent study showed predominant serous component with equal presentation of homologous and heterologous mesenchymal components.



**Fig. 1. H&E 100X showing both the carcinomatous and sarcomatous components with presence of necrosis in the lower field**

Eosinophilic hyaline granules are found in carcinosarcomas and are positive on periodic acid-Schiff staining with a minority immunoreactive for  $\alpha$ 1-antitrypsin [19]. Singular cases have been reported with trophoblastic or neuroendocrine differentiation or alpha-fetoprotein (AFP) expression [33].



**Fig. 2. Showing different histopathological components of carcinosarcoma of the ovary**

Due to lack of standardized data on histopathological analysis, the prognosis of predominant epithelial and mesenchymal components is still controversial and needs detail analysis at molecular level with large data for evaluation and to draw a conclusion.

Immunohistochemical examination is used for confirmation of diagnosis in carcinosarcoma. It is an important tool in highlighting biphasic nature and areas of heterologous differentiation which may give a prognostic impact [6]. Cytokeratin and epithelial membrane antigen are positive for epithelial component. Vimentin, smooth muscle actin, CD10, desmin, and myoglobin are positive in mesenchymal components (Fig. 3). S100 is used to detect chondroid or adipose tissue differentiation [5]. CD34 marker distinguishes ovarian carcinosarcomas from Epithelioid sarcomas, which strongly express CD34 [6]. P53 immunostain shows positivity in both carcinomatous and sarcomatous components which may suggest monoclonal theory [6].

## 5. CLINICAL DIAGNOSIS

### 5.1 Clinical Features

Ovarian carcinosarcoma follows a distinct natural history compared to other epithelial ovarian carcinomas [5,13,16], tends to occur in older women with more often presents at disseminated disease and with inferior prognosis. The majority have predilection for early dissemination [5,8,13,16,17]. The way of clinical presentation is similar to epithelial ovarian malignancy. Abdominal distension and pain, nausea, vomiting and weight loss are common symptoms. Palpable mass and ascites are common clinical findings. Epithelial and mesenchymal components behave in independent manner particularly in metastatic patterns. Transperitoneal spread is exclusively occurs by

epithelial component and rarely occurs by sarcomatous component [32]. Metastases usually involve serosal and peritoneal seeding. A recent study showed increased liver parenchymal metastases in comparison to classical epithelial ovarian carcinoma; the pelvic recurrence, liver metastases and peritoneal metastases are 31%, 23% and 19% respectively [34]. Carcinosarcomas present with larger tumour size typically ranging from 15-20 cm in diameter [13]. A recent study showed the size of the tumours range from 8-12 cm with mean size of 10.5 cm [6].

### 5.2 Serum Markers

Tumour marker CA125 is elevated in 74% of patients. AFP marker is rarely elevated [35]. In a study by Menon et al. [21] preoperative CA125 was raised in 9 out of 12 cases of ovarian carcinosarcoma and ascitic fluid cytology analysis revealed adenocarcinomatous deposits. In a case report by Patnayak et al. [31] CA125 was elevated.

### 5.3 Imaging Studies

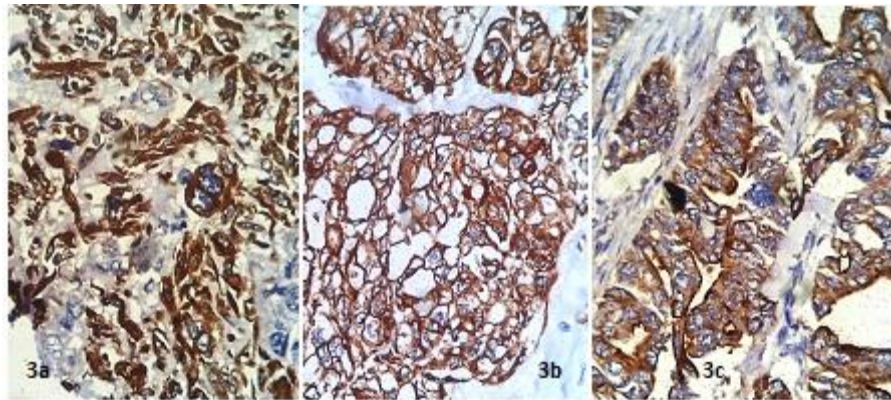
Ultrasonography is the initial radiological investigation of choice. Ultrasonographically tumours are large, composed of solid, cystic or mixed components with thick septa. MRI of abdomen describes the better characteristics of the tumour.

Staging classification system is similar to FIGO system applied to the other ovarian carcinosarcomas [36].

Preoperative diagnosis of the primary ovarian carcinosarcoma remains a challenging situation. Both the clinical and radiological findings are not specific for ovarian carcinosarcoma and are similar to other ovarian malignancies [37].

**Table 1. Showing predominant epithelial and mesenchymal components in carcinosarcoma of ovary**

Literature	Predominant carcinomatous component	Predominant sarcomatous component
Boucher et al. (1994) [22]	Endometrioid = serous	Heterologous (chondromatous and rhabdomyoblastic)
Kunkel et al. (2012) [30]	Serous component	Heterologous chondromatous
Menon et al (2013) [21]	Endometrioid component	Heterologous rhabdomyosarcomatous component
Patnayak et al. (2010)	Serous	Heterologous rhabdomyosarcomatous component
Rama K et al. (2015) [6]	Serous	Heterologous = homologous



**Fig. 3. Showing immunohistochemistry stain positive for: 3a) Vimentin in the sarcomatous component, 3b) Pan CK in the epithelial components, and 3c) EMA in the epithelial components**

There is no specific serum marker for ovarian carcinosarcoma and also cytological analysis of ascitic fluid may not give relevant components for carcinosarcoma. Data showed cytological analysis of ascitic fluid in positive cases yields malignant epithelial components in the majority cases [38]. The definitive diagnosis of carcinosarcoma can only possible by histopathological examination of the resected specimen.

#### 5.4 Treatment

Standard treatment consists of bilateral salpingo-oophorectomy, total abdominal hysterectomy, debulking of peritoneal metastases, and lymphadenectomy [17,18,25]. Treatment of ovarian carcinosarcoma is based upon FIGO staging. In stage I, total hysterectomy plus bilateral salpingo-oophorectomy, omentectomy, lymphadenectomy, and removal of any suspicious mass should be performed. In other stages, cytoreductive surgery should be performed like in other ovarian malignancies. The role of cytoreductive surgery is well established in epithelial ovarian carcinoma; but in carcinosarcoma it is still doubtful due to insufficient data. Recently Gynaecological oncology group (GOG) reported platinum as first line treatment with good response [36]. The role of radiation therapy is still not established [36].

Till date there is no consensus regarding optimal adjuvant chemotherapy regimens in ovarian carcinosarcoma. Many chemotherapeutic regimens already have been used in different centres without any standard conclusions. Women with ovarian carcinosarcoma have

relatively less response to chemotherapy than epithelial ovarian cancers [17]. According to GOG, poor response rate and high toxicity with doxorubicin for ovarian carcinosarcoma. Most chemotherapeutic regimens are simplified into platinum containing regimens versus non-platinum containing regimens. Many institutions follow ifosfamide with platinum based combination regimen while others follow taxane with platinum based combination regimen. Both the ifosfamide [39] and platinum [40-42] have demonstrated efficacy in both ovarian and endometrial carcinosarcoma. Carboplatin and paclitaxel combination chemotherapy regimen has a response rate up to 72% in carcinosarcoma of the reproductive tract with more favourable toxicity profile than ifosfamide and platinum regimen [43-45]. Current idea regarding adjuvant chemotherapy is still unclear but with increased trend for favouring platinum-based therapy [46]. Literature showed 68% overall response rate in the platinum containing regimens and 23% response rate in non-platinum containing regimens [44,47]. In an analysis of 22 patients, treatment with carboplatin and paclitaxel versus cisplatin and ifosfamide found no survival difference [48]. Rutledge and co-workers found improved survival in women with ovarian carcinosarcoma treated with ifosfamide combination regimen [49]. According to Chun et al, women who received paclitaxel/platinum-based combination chemotherapy had longer progression free interval and overall survival [10]. According to Paulsson et al. [50] a retrospective series of 81 Swedish cases demonstrated that, compared to those with an incomplete regimen, the 57% of subjects who completed 6 cycles of platinum based chemotherapy had improved

overall survival. Combination chemotherapy regimen with cisplatin/ifosfamide, and also paclitaxel/carboplatin have been tried in some studies with details [15,29,43,48,51-53].

A recent study shows lack of response to inhibitors of epithelial growth factor receptor (EGFR), vascular endothelial growth factor receptor (VEGFR), insulin growth factor-1 receptor (IGF-1R), and poly ADP-ribose polymerase (PARP) indicating insufficiency of gene expression and amplification profiling to predict response [54]. Model patient heterotransplant #003 (PH003), and future ovarian carcinosarcoma tumour graft models, may be helpful to analyse for better novel therapies to improve survival outcome [54].

### 5.5 Prognosis

MMMT is an aggressive tumour with poor survival outcome. MMMT of ovary carries more favourable prognosis than that of the uterus [18] but with worse prognosis in comparison to serous carcinoma of the ovary [17,55,56]. A case-control study with 50 women of ovarian carcinosarcoma showed 24 months of overall median survival, inferior to 41 months for women with serous carcinomas [5]. One study showed inferior survival for ovarian carcinosarcoma with advanced stage disease in comparison to that of serous carcinomas whereas no statistically significant difference in survival between these two histologic subtypes for early stage diseases was identified [16]. In a recent study survival is inferior for all the stages of ovarian carcinosarcomas in comparison to serous carcinomas and survival was only 65% for carcinosarcomas stage I whereas 81% for those with serous carcinomas [3]. It is an aggressive subtype of epithelial cancer diagnosed at advanced stage [7,52,55,57]. The median survival is 8-16 months in MMMTs [25]. In the majority of studies, the median survival was nearly 18 months [18,20,27,29-31,41,52]. The age and stage are associated with overall survival [7,10,17,43,58]. Age >70 years carries a significantly worse prognosis than younger patients [34]. Heterologous sarcoma component and high grade lack of differentiation of the epithelial component are two poor histological prognostic factors [12]. Also, the extent of cytoreductive surgery and residual status correlate with outcome [59]. Some literatures reported inferior prognosis associated with higher residual tumour burden [15,17,25,43,49,60]. According to previous data, the optimal

cytoreduction means  $\leq 2$  centimeters diameter of residual disease remaining [17,43,44,57,58]. But recently the optimal cytoreduction means no longer than 1 centimeter in diameter of residual disease after primary surgery [61]. It is better if no gross residual disease after cytoreductive surgery [16]. In a retrospective study of ovarian carcinosarcoma by Rauh-Hain et al. [5] patients with microscopic residual disease had OS of 47 months, those with macroscopic residual disease  $\leq 1$ cm had OS of 18 months and those with suboptimal cytoreduction had OS of 8 months. Patients treated with optimal cytoreduction had a median survival of 25 months whereas it was 8 months in cases with suboptimal cytoreduction [62].

**Table 2. Adverse prognostic factors**

Advanced age
Advance stage
Predominant epithelial tumours
Predominant serous subtype [25]
Heterologous elements [63]
Suboptimal cytoreductive surgery
Post operative higher residual disease burden
Poor response to therapy

### 6. CONCLUSION

MMMT of ovary are rare tumours with aggressive behaviour, the majority present at an older age, advanced stage at the time of diagnosis and survival varies with stage of the disease and histological types. Despite all aggressive modalities of treatment there is increased risk of death with poor prognosis in comparison to epithelial ovarian carcinoma. Such rare disease with poor prognosis needs more number of prospective studies to better understand the molecular characteristics of MMMT and to suggest new therapeutic regimens to improve survival of the patients.

### CONSENT

It is not applicable.

### ETHICAL APPROVAL

It is not applicable.

### COMPETING INTERESTS

Authors have declared that no competing interests exist.

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